ATTACHMENT TO ADVISORY ACTION

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 02/24/10 in response to the final Office Action mailed 11/24/09.

Status of Claims

2) Claims 1, 4-6, 8, 33, 36, 38, 47, 48, 53 and 54 have been amended via the amendment filed 07/13/09.

Claims 3 and 37 have been canceled via the amendment filed 02/24/10.

Claims 1, 4-9, 33-36 and 38-54 are pending and are under examination.

Petition Denied

3) It is noted that Applicants' petitions filed 12/22/09 and 01/05/2010 requesting withdrawal of the finality of the Office Action mailed 11/24/2009 have been denied by the Office.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Moot

6) The rejection of claims 3 and 37 made in paragraph 23 of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, first paragraph, as containing inadequate written description, is moot in light of Applicants' cancellation of the claims.

7) The rejection of claims 3 and 37 made in paragraph 25 of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

Rejection(s) Withdrawn

6) The rejection of claims 47 and 53 made in paragraph 23 of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, first paragraph, as containing inadequate written description, is withdrawn.

8) The rejection of claim 5 made in paragraph 25(a) of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

9) The rejection of claim 53 made in paragraph 25(b) of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

10) The rejection of claim 1 made in paragraph 25(c) of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

11) The rejection of claims 5, 47 and 53 made in paragraph 25(d) of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

12) The rejection of claims 5, 47 and 53 made in paragraph 25(e) of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn.

13) The rejection of claim 7 made in paragraph 25(h) of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn.

14) The rejection of claims 4, 6 and 33-36 made in paragraph 25(i) of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn.

Rejection(s) Maintained

15) The rejection of claims 1, 4, 7-9, 33-35, 38-44 and 49-51 made in paragraph 23 of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, first paragraph, as containing inadequate written description, is maintained for the reasons set forth therein and herein below.

Applicants' arguments have been carefully considered, but are not persuasive.

Applicants acknowledge the Office's citation of Colman P.M. (*Research Immunol.* 145:33-36, 1994) teaching the effect of an amino acid alteration on peptide-antibody interaction, and McGuiness *et al.,* (*Mol. Microbiol.* 7:505-514, Feb 1993); and McGuiness *et al.,* (*Lancet* 337:514-517, March 1991) teaching that a change of a single amino acid can disrupt antibody-polypeptide binding; and of von Eiff *et. al.* (*Diagn. Microbiol. Infect. Dis.* 58:297-302, 2007). Applicants allege that the rejection improperly characterizes and discounts the data provided in the application; requires the immunogen described in the claims to provide protective immunity against every possible *S. aureus* in a non-human or human host, and for claims referencing a patient requires the immunogen to be effective against immunosufficient, immunodeficient and immunocompromised patients; and is based on the possibility of an amino acid alteration disrupting an antibody-protein interaction without taking into account the likelihood such a disruption would occur within a polypeptide epitope and would render the polypeptide no longer protective. Applicants cite case law and submit that the data and guidance provided in the present application reasonably conveys to those skilled in the art that applicants were in possession of claimed protective immunogens, when the application was filed. The data provided in the application allegedly demonstrates that applicants were in possession of the protective immunogens covered in the claims. Applicants state that Example 3 provides protection data using different polypeptides wherein *S. aureus* strain Becker was used as the challenge strain; Example 6 illustrates the use of a *full-length construct* to provide protection against different clinical isolates; and Example 16 illustrates the use of different polypeptides to provide protection. Applicants state that the provided protection data was generated employing different constructs such as SEQ ID NO: 3, SEQ ID NO: 4 containing a carboxyl His-Tag, SEQ ID NO: 5 containing a carboxyl His-Tag, and SEQ ID NO: 28 (corresponding to a full-length sequence with a His-Tag). Applicants submit that SEQ ID NOs: 1 and 5 provide a protective region corresponding to an ORF0657nl region and that SEQ ID NOs: 3 and 4 provide a protective region corresponding to an ORF0675nH region. Applicants state that SEQ ID NOs: 3, 4, and 5 are covered by at least independent claims 1 and 8.

Applicants discuss Figures 2A-2E as well as Example 6 and Figures 4A-4H, the latter pertinent to the polypeptide of SEQ ID NO: 28 and its protection against different strains *S. aureus* and conclude that the ability of a *full-length* ORF0657n to provide protective immunity

against different clinical isolates confirms the expectation that alterations can be made to a reference sequence provided in one or more claims, where the resulting polypeptide retains its protective ability. Applicants state that the submitted Attachment A is a sequence comparison of SEQ ID NOs: 1, 3, 4, 5 and 28, wherein the leader sequence and the sortase cleavage site are noted in the sequence comparison. The sequence comparison is said to also highlight amino acids at a couple of variable amino acids present in SEQ ID NOs: 1, 3, 4, 5 and 28. Figures 2A-2E, present in the filed application, is stated as providing a sequence comparison of different ORF0657n sequences across the ORF0657nH region and includes SEQ ID NOs: 1, 3, 4, and 5. Appendix A is stated as providing a useful illustration of the SEQ ID NO: 28 region expected to be involved in producing protective immunity, the leader sequence and LPXTG being cleavage points during cellular processing. Applicants state that the SEQ ID NO: 28 region expected to be present in the cell wall corresponds approximately to the ORF0657nH region of SEQ ID NO: 3 and that the expected SEQ ID NO: 28 cell wall region has four additional carboxyl amino acids than SEQ ID NO: 3. Applicants note that SEQ ID NO: 1 runs across 78% of SEQ ID NO: 28.

Applicants state that Example 3 illustrates the ability of polypeptides of SEQ ID NOs: 4, 5 and 28 to provide protection against *S. aureus* strain Becker, the results being provided in Figures 3A-3C. Applicants note that SEQ ID NOs: 4 and 5 employed in Example 3 also contained a His-Tag. The brief description of Figures 3A, 3B, and 3C is stated as referring to the use of strain Becker. The full-length ORF0657n of *S. aureus* strain Becker is said contain 95% sequence identity to the full-length ORF0657n COL sequence (SEQ ID NO: 2); and SEQ ID NOs: 1, 3, 4, 5 and 28 are said to be based on the COL sequence. Applicants state that SEQ ID NOs: 4 and 5 are within the scope of at least independent claims 1 and 8 and that the ability of immunogens containing these sequences to provide protective immunity against *S. aureus* strain Becker demonstrates that the exact sequence employed as a protective immunogen in the example is not critical. Applicants assert that based on random chance, one of ordinary skill in the art would expect the differences between *S. aureus* strain Becker and COL to be located in different regions including the OFR0657nI and ORF0657nH regions. Applicants submit that Figures 2A-2E confirm such expectation by providing evidence that differences among different ORF0657n present in different strains occur in different locations including the OFR0657nI region and the ORF0657nH region. Appendix B is stated as providing a sequence comparison

between the strain Becker ORF0657n, SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5 and apparently it confirms the evidence provided in the application, and what would be expected by one skilled in the art concerning the presence of different alterations between COL and Becker being located in different regions. Applicants argue that the ability of SEQ ID NOs: 4 and 5 to provide protective immunity against the heterologous *S. aureus* strain Becker provides important evidence that alterations to the sequences used in the application could be made and resulting immunogens would be protective. Applicants further argue that the skilled artisan could expect *the naturally occurring sequence* present in the *S. aureus* Becker strain to provide protective immunity against at least strain Becker and that such an expectation of protection is based on, for example, a polypeptide providing a ORF0657nI or ORF0657nH region based on strain Becker having a greater degree of homology to strain Becker ORF0657n than SEQ ID NOs: 4 or 5.

Applicants point to Table 3 and assert that CL-10, CL-13, CL-30, CL-18 and CL 21 are diverse *S. aureus* strains with different degrees of sequence identity to SEQ ID NO: 2. Applicants state that CL-10 has a 97% sequence identity to SEQ ID NO: 2, CL-13 has a 99% sequence identity to SEQ ID NO: 2, CL-21 methicillin resistant strain with a 94% sequence identity to SEQ ID NO: 2, and CL-30 has a 96% sequence identity to SEQ ID NO: 2. Applicants argue that based on the data and guidance provided in the application, the skilled artisan would expect *the naturally occurring* ORF0657nl or ORF0657nH region present in the *S. aureus* strain used as a challenge strain, to provide protective immunity against the challenged strain. Applicants contend that based on Figures 4A-4H, the corresponding ORF0657nI or ORF0657nH region from CL-10, CL-13, CL-30, CL-18 and CL 21 would at least be expected to provide protection against the homologous strain.

Applicants point to Example 16 and Figure 10 and submit that the polypeptide providing an ORF0657nI region generated a similar level of protection to the polypeptide providing the ORF0657nH region indicating that ORF0657nH (SEQ ID NO: 3 and 4) and ORF0657n (SEQ ID NO: 28) do not contain a critical region beyond that provided by the ORF0657nl region (SEQ ID NO: 5 containing a His-Tag). Applicants state that while not indicated in the application, the challenge strain used in Example 16 was strain Becker of *S. aureus*. With this, Applicants opine that polypeptides having a high degree of structural similarity are expected to have similar

properties. Applicants assert that the application provides an expectation that polypeptides covered by the claims will be protective. Applicants allege that the rejection fails to provide any indication as to why a significant number of polypeptides within the scope of the claims having a sequence structurally related to a protective polypeptide would not provide protection. Applicants state that the cited references concern *spa* and capsular polysaccharides, and the potential effect of an amino acid alteration on peptide-antibody interaction and that the ORF0657n target is a polypeptide, not a polysaccharide. Applicants assert that the references concerning antibody-peptide interactions are silent as to the likelihood that a particular alteration would prevent a polypeptide over 410 amino acids in length, shown to be protective, from maintaining its ability to provide protection, and that the possibility that some unknown alteration in an amino acid residue may impact a particular protein-antibody interaction, does not necessarily equate to a polypeptide within the scope of the claims losing its ability to provide protective immunity. Applicants argue that SEQ ID NO: 1 is 446 amino acids in length and speculate that it may contain more than one epitope providing a beneficial effect.

Applicants' arguments have been carefully considered, but are not persuasive.

The elected polypeptide species examined in the instant application is SEQ ID NO: 1. The purified polypeptide immunogen claimed in claim 1(b) and recited in claim 8(b) is minimally required to (A) *consist* of a *fragment* of an amino acid sequence 94% identical to SEQ ID NO: 3, wherein the *fragment* comprises an amino acid sequence 94% identical to SEQ ID NO: 1 (i.e., 6% non-identical); and (B) provide protective immune response against *S. aureus*. The generic limitation 'protective immune response against *S. aureus*' in claim 1 does not specify to whom the protective immune response is provided. The immunogen claimed in claim 7 is minimally required to (A) consist of an amino acid sequence 90% identical to SEQ ID NO: 1 (i.e., 10% non-identical) and one or more additional regions covalently joined thereto at the carboxyl or the amino terminus as recited therein; and (B) provide protective immune response against *S. aureus*. Although claim 7 does not include the recitation of providing 'protective immune response against *S. aureus*', the limitation 'immunogen' as defined at line 25 of page 2 of the specification is required to have the ability to provide protective immunity, consistent with the intended prophylactic (i.e., vaccine) applications. As set forth previously, the claims encompass a vast genus of polypeptide immunogen variants that are fragment variants of SEQ

ID NO: 3 which are further variants of SEQ ID NO: 1, having up to 6% non-identity to SEQ ID NO: 3 and SEQ ID NO: 1 (claims 1 and 8), and immunogen variants with up to 10% non-identity to SEQ ID NO: 1 (claim 7), each having the requisite ability to provide protective immunity against *S. aureus*. Any amino acids may be substituted, modified, or deleted along the length of SEQ ID NO: 3 and/or SEQ ID NO: 1 as long as the polypeptide fragment retains the percent identity as recited, with or without the further up to 25 amino acid additions. The amino acid sequence of SEQ ID NO: 2 is the *full-length* polypeptide. The full-length polypeptide was known in the art at the time of the invention as taught by Foster *et al*. Applicants have acknowledged previously that full-length ORF0657n sequence is *excluded* from the claimed invention. For example, at third full paragraph on page 9 of the amendment/remarks filed 08/18/08, Applicants stated the following [Emphasis added]:

> 'Claim 1 **excludes** SEQ ID NO: 2'.

Again, at first full paragraph on page 20 of Applicants' amendment/remarks filed 03/13/09, Applicants stated the following [Emphasis added]:

> Claims 1, 5, 7, and 8 were amended as discussed above, so that **the full-length ORF0657n sequence is <u>not</u> covered.** Claims 3, 4, 6, 7, 33-35, and 37-44 as previously presented provided for less than the full-length sequence.

Thus, by Applicant's own admission, SEQ ID NO: 2 is not covered by claims 1, 5, 7 and 8. With regard to Applicants' remarks on SEQ ID NO: 28, SEQ ID NO: 28 is the *full-length* SEQ ID NO: 2 modified at the amino terminus and at the carboxyl terminus. Accordingly, since SEQ ID NO: 2 is excluded from the instant claims, SEQ ID NO: 28 of the instant specification, which is longer than SEQ ID NO: 2, is also excluded from claims 1, 5 and 8 as well as claim 7. As Applicants have acknowledged, the ORF0657nI region of SEQ ID NO: 1 that overlaps with a portion of SEQ ID NO: 28 is 78% of SEQ ID NO: 28. See second paragraph on page 11 of Applicants' amendment/remarks filed 02/24/2010. Furthermore, SEQ ID NO: 28, SEQ ID NO: 2, and the sequences depicted in Figure 2A-2E are *not* a fragment of a polypeptide immunogen consisting of SEQ ID NO: 3 or a 94% variant of SEQ ID NO: 3, and therefore do not fall within the scope of claims 1(b) and 8(b). SEQ ID NO: 28 and SEQ ID NO: 2 are excluded from claim 7 as well. The SEQ ID NO: 4 and SEQ ID NO: 5 polypeptide immunogen species are not 94% or 90% identical variants of SEQ ID NO: 1. SEQ ID NO: 3 is not a fragment of SEQ ID NO: 3 as required by claims 1(b) and 8(b). The SEQ ID NO: 3 polypeptide species is not a 94% or 90%

identical variant of SEQ ID NO: 1. Furthermore, the ORF0657nI-equivalent region of SEQ ID NO: 2 or SEQ ID NO: 28 does not constitute a 90% or 94% identical variant species of SEQ ID NO: 1.

Contrary to Applicants' assertion, the ability of SEQ ID NOs: 4 and 5 to provide protective immunity against the heterologous *S. aureus* strain Becker does not show a structure-function (i.e., protective function) correlation for a sufficient number of polypeptide immunogen species representative of the claimed vast genus consisting of a fragment of an amino acid sequence with up to 6% non-identity to SEQ ID NO: 3, wherein the fragment comprises an amino acid sequence with up to 6% non-identity to SEQ ID NO: 1, and a structure-protective function correlation for a sufficient number of claimed immunogen species representative of the huge genus consisting of an amino acid sequence with up to 10% non-identity to SEQ ID NO: 1 and having one or more regions covalently joined thereto. With regard to claims 1(b) and 8(b), SEQ ID NO: 5 is a purified polypeptide immunogen species consisting of an amino acid sequence 99.8% identical to SEQ ID NO: 1 which provides protective immunity in a mammal capable of being infected with *S. aureus*. With regard to claims 1(b) and 8(b), SEQ ID NO: 4, being longer than SEQ ID NO: 3, does not meet the limitation 'purified polypeptide immunogen consisting of a *fragment* of an amino acid sequence at least 94% identical to SEQ ID NO: 3'. Furthermore, SEQ ID NO: 4 or SEQ ID NO: 5 is a purified polypeptide immunogen species consisting of an amino acid sequence 99.8% identical to SEQ ID NO: 3 and SEQ ID NO: 1. Therefore, these two species do not establish possession of a sufficient number of polypeptide or immunogen species consisting of an amino acid sequence 90% to 98% identical to SEQ ID NO: 3 and SEQ ID NO: 1, while having the capacity to provide protective immunity in a human or non-human. Therefore, these sequence species do not form sufficient members of the claimed huge genus of purified and non-purified or non-isolated polypeptide immunogen consisting of the fragment recited in part (b) of claims 1 and 8, encompassing 94% identical variants of SEQ ID NO: 1, or for the genus of 90% identical immunogen variant species of SEQ ID NO: 1 as claimed in claim 7.

Contrary to Applicants' assertion, the Office did show why a significant number of polypeptide variants within the scope of the claimed invention having the recited sequence identity would not provide protection. With regard to this and with regard to Applicants' opinion

that polypeptides having a high degree of structural similarity are expected to have similar properties, the following evidence within the instant application must be noted. The instant application at third full paragraph of page 8 states that a fragment of SEQ ID NO: 2 consisting of amino acids 82-486 or 42-196 was **not** protective. See Figure 1A. The amino acid residues 42-609 of SEQ ID NO: 2 constitute SEQ ID NO 1. The sequence consisting of the amino acids 82-486 of SEQ ID NO: 2 having as high as 91% structural identity to SEQ ID NO: 1 and falling within the scope of claims 7 and 53 has been demonstrated to be non-protective. See third full paragraph of page 8; Figure 1A; and the brief description of the drawing for Figure 1A. Applicants have reemphasized this lack of protection by fragments of SEQ ID NO: 1 made up of amino acids 82-486, 42-196 and 461-609 of the full-length SEQ ID NO: 2 at page 8 of Applicants' amendment/remarks filed 08/18/08. Therefore, the evidence from Applicants' own disclosure establishes that a polypeptide having as high as 91% structural identity to SEQ ID NO: 1 cannot be expected to have similar protective properties. This is clearly indicative of the unpredictability in obtaining a polypeptide species that is about 10% non-identical in structure to SEQ ID NO: 1 which concurrently remains protective against *S. aureus*. Furthermore, SEQ ID NO: 4, a polypeptide immunogen species 99.8% identical to SEQ ID NO: 1 when His-tagged at the carboxyl terminus, showed what appears to be a statistically insignificant protection, compared to the protection induced by AHP alone, against the Becker strain of *S. aureus* in BALB/C mice, even upon administration with the AHP adjuvant. See Figure 3B. Contrary to Applicants' speculation, the ability of SEQ ID NOs: 4 and 5 to provide protective immunity against *S. aureus* strain Becker demonstrates that it is critical for the claimed sequence species to have at least 99.8% sequence identity to SEQ ID NO: 1. Figure 1A not only illustrates that a polypeptide immunogen consisting of an amino acid sequence having as high as 91% identity to SEQ ID NO: 1 is **not** protective, but further provides the evidence for the lack of a single, let alone more than one, protective epitope therein. Figure 1A establishes that the unmodified or unaltered SEQ ID NO: 1 when merely split into a fragment of amino acids 82-486, or amino acids 42-196, looses its protective capacity, clearly indicating the criticality of retaining the amino acid residues of the SEQ ID NO: 1 core sequence intact within the claimed fragment in order to retain the requisite function of providing protective immunity against *S. aureus*. Thus, not only is there a lack of structure-function correlation for a representative number of claimed

polypeptide immunogen variant species falling within the claimed huge genus, there is also a lack of predictability as to whether polypeptide variants having up to 6 or 10% non-identity to SEQ ID NO: 1 anywhere along SEQ ID NO: 1 would remain immunospecific to *S. aureus* and provide protective immunity against *S. aureus* in a human or a non-human host. Contrary to Applicants' speculation, the ability of SEQ ID NOs: 4 and 5 to provide protective immunity against *S. aureus* strain Becker demonstrates that it is critical for the claimed sequence species to have at least 99.8% sequence identity to SEQ ID NO: 1.

What are claimed currently are not *S. aureus* strains with *the naturally occurring* polypeptide immunogen *consisting* of ORF0657nl or ORF0657nH region providing protective immunity against the challenged strain, but polypeptide immunogens *consisting* of up to 6% or 10% non-identity to SEQ ID NO: 1, or differing from SEQ ID NO: 1 by up to 25 amino acid alterations, having the capacity to provide protective immunity against any *S. aureus* in any host including a human patient. Since the immnuogen claimed in claim 7 is not required to be purified, it encompasses non-isolate and non-purified immunogens and reads on *S. aureus* strains consisting of SEQ ID NO: 1 or its 94% identical variants. However, Applicants were not in possession of *S. aureus* strains containing naturally occurring ORF0657nl or ORF0657nH region. The state of the art at the time of the invention does not document the existence of such *S. aureus* strains in nature. Furthermore, without the knowledge or specific disclosure on whether or not the ORF0657nl or ORF0657nH region is buried in the cell wall or surface-exposed partially or fully, a skilled artisan would not expect *S. aureus* strains containing allegedly naturally occurring ORF0657nl or ORF0657nH region to be protective. The Office agrees with the Applicants that SEQ ID NO: 3, 4 and 5 are the tested sequences that are covered by instant claims 1 and 8. These sequences are also covered by claim 7. However, these sequences are representative of 99.8% identical variant species of SEQ ID NO: 1, but not 90% or 94% iden5tical variant species. Of these three polypeptide immunogen species falling within the scope of the claims 1 and 8 that have been tested for protection, none have been correlated with homologous protection, and therefore the ability of the corresponding ORF0657nI or ORF0657nH region from CL-10, CL-13, CL-30, CL-18 and CL 21 to provide protection against the homologous strain is not predictable. There is no evidence that native or altered COL sequence variants were tested for protection against the COL strain of *S. aureus*. For example,

Figure 1A depicts polypeptides that were tested in animals and found to be protective (shown by filled rectangles) and polypeptides tested and found not to be protective (shown by open rectangles). Of these, the ORF0657nI species (potentially SEQ ID NO: 1) falling within the scope of the instant claims is said to be protective. Whether or not this protection was conferred against homologous or heterologous strain of *S. aureus* is not disclosed. If this ORF0657nI species is indeed SEQ ID NO: 1, it represents a polypeptide immunogen consisting of an amino acid sequence 100% identical to SEQ ID NO: 1 which provides protective immunity against a strain of *S. aureus* in an animal. However, this single species is not representative of the huge genus of the claimed polypeptide immunogen variant species or immunogen variant species consisting of an amino acid sequence up to 10% or 6% non-identity with SEQ ID NO: 1 and having the capacity to provide protective immunity against *S. aureus* in a human or non-human patient. This is critically important because the polypeptide depicted as fragment 2 in Figure 1A via one of the open rectangles consists of amino acids 82-486 of SEQ ID NO: 2, spans over a major portion of SEQ ID NO: 1, serves as a polypeptide consisting of an amino acid sequence that is about 91% identical to SEQ ID NO: 1, yet was found **not** to be protective. See first full paragraph on page 5 of the instant specification.

It should be noted that the percent identity recited in the instant claims is relative to SEQ ID NO: 1, not SEQ ID NO: 2. The CL-10, CL-13, CL-30, CL-18 and CL 21 sequences do not constitute polypeptide immunogen species consisting of an amino acid sequence 94% identical to SEQ ID NO: 1, or immunogen species consisting of an amino acid sequence 90% identical to SEQ ID NO: 1 with up to 20 additional amino acids at its carboxyl or the amino terminus. The SEQ ID NO: 1-corresponding regions of these sequences do not constitute polypeptide immunogen species consisting of an amino acid sequence 94% identical to SEQ ID NO: 1, or immunogen species consisting of an amino acid sequence 90% identical to SEQ ID NO: 1 with up to 20 additional amino acids at its carboxyl or the amino terminus. Moreover, immunogens from none of these CL-10, CL-13, CL-30, CL-18 and CL 21 sequences corresponding to the SEQ ID NO: 1 region have been correlated with homologous or heterologous protection, with or without an adjuvant. Given the functional unpredictability documented in the instant application via the lack of protection by fragments 1-3, particularly fragment 2 as illustrated in Figure 1A, given the demonstration of a statistically insignificant protection by SEQ ID NO: 4 against the

Becker strain despite its 99.8% identity to SEQ ID NO: 1 (Figure 3B), and given the lack of protection by one of the ORF0657nI itself, with no amino acid alterations therein, in the absence of an adjuvant such as endotoxin (see additional data), one of skill in the art would not recognize that Applicants were in possession of a representative number of the protective polypeptide immunogen variant species or the protective immunogen variant species currently encompassed within the scope of claims.

The Office has previously set forth sufficient rationale and has established a clear lack of written description. Contrary to Applicants' assertion, no requirements were made for illustration of the ability of the claimed polypeptide to provide protective immunity against each and every *S. aureus* in a non-human or human host, including immunosufficient, immunodeficient and immunocompromised patients. Instead, the Office action analysed and set forth the scope of the claims under 35 U.S.C 112, first paragraph as required. The reference of von Eiff *et. al.* was properly cited to document the existence immunologically heterogeneous or distinct types among *Staphylococcus aureus*.

Contrary to Applicants' assertion, the naturally occurring sequence present in the *S. aureus* Becker strain is not covered by the instant claims similar to the naturally occurring sequence from COL strain. The as-filed specification provides no structure-protective function correlation for a polypeptide or immunogen consisting of the Becker ORF0657n sequence. At the time of the invention, Applicants were not in possession of a polypeptide or immunogen consisting of the Becker ORF0657n sequence that provided protective immunity against any strain of *S. aureus* in an animal or a human patient. In fact, the strain Becker ORF0657n sequence is not a part of the instant application and the sequence listing. Attorney Heber confirmed that the Becker ORF0657n sequence is not a part of the instant application in a telephone communication on 03/08/2010.

The issue of host species in which protective immunity against *S. aureus* is to be induced is very relevant to the unpredictability issue, in light of Applicants' own additional data made of record. Note that the generic limitation 'protective immunity against *S. aureus*' in claim 1 does not specify to whom the protective immune response is provided, and therefore broadly encompasses said response in any host species. The instant specification and Applicants' additional data made of record concretely establish that the species falling within the scope of the

claims and the full-length modified His-tagged SEQ ID NO: 2 (SEQ ID NO: 28) were protective in one host species only when administered with the AHP adjuvant. The additional data provided on 08/18/2008 further documents that the ORF0657nI did not provide protection in BALB/C mice in the absence of the endotoxin adjuvant. See pages 7 and 8 of Applicants amendment/remarks filed 08/18/08. If this result is to be extrapolated to a human patient, including an immunodeficient, immunosuppressed and immunocompromised human patient, even the ORF0657nI corresponding to the claimed polypeptide immunogen consisting of the recited amino acid sequence, let alone its 94% or 90% identical variants, would not be expected to be protective in human patients on its own. Note that the composition of claims 8 and 38-48 and the immunogen of claims 1, 4-7, 33-36 and 49-54 do not contain an adjuvant and are still required to provide protective immunity against *S. aureus* in an unspecified host, or in a human and/or non-human patient.

It is important to note that the recited amino acid alterations are not limited to amino acid additions at the amino or the carboxyl terminus of SEQ ID NO: 1, but include alterations, substitutions, and deletions within SEQ ID NO: 1. The Office has previously established that polypeptides having any degree of structural similarity are not necessarily expected to have similar properties absent a concrete structure-function correlation. With regard to Applicants' argument that the rejection is based on the possibility that an alteration to a critical amino acid within the 446 amino acids of SEQ ID NO: 1 may impact a protein antibody interaction, the following should be noted. As set forth previously, for an altered polypeptide to be protective, it has to minimally bind immunospecifically with a protective antibody specific to the native polypeptide. Therefore, interaction between a protein and its specific protective antibody is very relevant for immunospecific protection. As set forth previously, the state of the art documents that a change of even a single amino acid residue can alter the folding of a polypeptide such that the antibody-binding region no longer recognizes the polypeptide. See right column on page 33 of Colman PM. *Research Immunol.* 145: 33-36, 1994, of record. Without such immunospecific recognition, there cannot be homologous or heterologous immunoprotection. It is recognized in the art that even a very conservative substitution may abolish binding. See first full paragraph on page 35 of Colman. Colman further taught that binding interactions could be considered less tolerant because the changes involved occur in what might be called the active site. See third full

paragraph on page 35 of Colman. The art reflects unpredictability as to which amino acids in a specific protein can be varied, i.e., replaced or added, without adversely affecting the functional properties of that specific protein. In other words, the retention of the immunospecificity following one or more amino acid substitutions, including conservative amino acid substitutions within a bacterial polypeptide is not predictable. For instance, McGuinnes *et al.* (*Mol. Microbiol.* 7: 505-514, Feb 1993, of record) taught that "[a] single amino acid change within an epitope, or an amino acid deletion outside an epitope, were both associated with loss of subtype specificity resulting from a change in the predicted conformation at the apex of the loop structure" in case of a meningococcal polypeptide. See abstract. Similarly, McGuinnes *et al.* (*Lancet* 337: 514-517, March 1991, of record) taught that a point mutation generating a single amino acid change in a P1.16-specific epitope in the VR2 region of the *porA* gene of a strain of *Neisseria meningitidis* of subtype P1.7,16 resulted in "striking changes in the structural and immunological properties of the class 1 protein" of this isolate. See abstract and page 514 of McGuinnes *et al.* Thus, the state of the art at the time of the invention documented the unpredictability in obtaining a functional variant of a microbial polypeptide that retains its specific immunological binding function(s). In an unpredictable art, adequate written description of a genus embracing widely variant species cannot be achieved by disclosing one species within the genus, but through sufficient description of a representative number of species within the claimed broad genus. In the instant case, possession of a sufficient number of species representing the huge genus has not been shown. The instant application does not provide an expectation that a representative number of polypeptide variant species covered by the full scope of the instant claims would be protective against *S. aureus*. The protein-antibody interaction is minimally needed for immunospecific protection since the antibodies induced by the polypeptide variants are required to first recognize the native polypeptide on pathogenic *S. aureus* cells and then confer protection against pathogenic *S. aureus*. Without a structure-function correlation and without the identification of one or more domains, or contiguous or discontiguous epitopes, linear or conformational epitopes within SEQ ID NO: 1 or its variants, responsible for providing protective immunity against a homologous or heterologous *S. aureus*, one of skill in the art would not recognize that inventors had possession of the full scope of the invention as claimed at the time of the invention. Applicants have not described which of SEQ ID NO: 1's amino acids

can be varied such that the polypeptide immunogen variant still maintains the capacity to provide such broad protective immunity. Without a convincing correlation between structure and function, the claims do little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *Ex parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. Appl. & Int. 2007) citing *Eli Lilly*, 119 F.3d at 1568, 43 USPQ at 1406 ('definition by function ….. does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is'). The instant claims do not meet the written description provision of 35 U.S.C. § 112, first paragraph. The rejection stands.

16) The rejection of claim 8 made in paragraph 25(f) of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for the reasons set forth therein and herein below.

Applicants contend that claim 8 is a composition claim, not a method of use claim, and that the preamble description of a patient indicates a possible use of the composition and is not a limitation necessitating the use of the immunogen in a patient. Applicants state that the reference to providing protective immunity in the body of the claim against *S. aureus* refers to a property of the composition consistent with the claim preamble.

Applicants' arguments have been carefully considered, but are not persuasive. Claim 8 continues to be vague and indefinite in the limitation: 'composition *able to induce a protective immune response against S. aureus in a patient* comprising an *immunologically effective amount of* a purified polypeptide immunogen *that provides protective immunity against S. aureus*'. The latter limitation 'provides protective immunity against *S. aureus'* does not specify that the protective immunity provided against *S. aureus* is --in said patient--, and therefore encompasses protective immunity provided against *S. aureus* in a non-patient, or a patient other than the one recited in line 2 of the claim. The recited '*immunologically effective amount of* a purified polypeptide immunogen *that provides protective immunity against S. aureus'* in a non-human patient or a human carrier need not induce a protective immune response against *S. aureus* in a human patient, AIDS patient, cancer patient etc. The rejection stands.

17) The rejection of claim 7 made in paragraph 25(f) of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for the reasons set forth therein and herein below.

Applicants contend that claim 7 refers to 'an amino acid sequence' and goes on to indicate that the one or more additional regions or moieties is covalently joined to 'said sequence.

Applicants' argument has been carefully considered, but it does not address the rejection. Claim 7 continues to be vague and indefinite in the limitation: 'facilitates polypeptide stability', because it is unclear the stability of which polypeptide is being facilitated by the one or more additional regions or moieties. The claim has no earlier recitation of any 'polypeptide'. The claimed immunogen is not purified and is expected to contain extraneous polypeptides in major or residual amounts. It is unclear the stability of which polypeptide is facilitated. The relationship to the claimed immunogen, if any, of the polypeptide whose stability is facilitated, is not understood. The rejection stands.

18) The rejection of claims 9 and 38-54 made in paragraph 25(i) of the Office Action mailed 11/24/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for the reasons set forth therein.

Remarks

19) Claims 1, 4, 7-9, 33-35 and 38-54 stand rejected.

The elected species that has been examined, SEQ ID NO: 1, in claims 5 and 6 is free of prior art of record. Although Applicants' amendment addresses the rejections of claims 5 and 6, an extension of examination to a non-elected species is needed, requiring further consideration and search of the next species. Due to the after-final stage of the prosecution, no new searches are performed.

Claim 36 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The limitation 'the carboxyl or the amino terminus' (see last line) in claims 5, 47 and 53 is to be interpreted as the carboxyl or the amino terminus of the recited amino acid sequence.

20) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

21) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

22) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

/S. Devi/
Primary Examiner
AU 1645

March, 2010